REMARKS

A. Status of the Claims

Claims 73, 78, 81-86, 88-98 and 100 are pending in the above-identified application. Claims 73, 78, 81-86, 88-98 and 100 stand rejected, and Claims 81, 92 and 95 are objected to, as discussed below. Claim 81 is amended to correct informalities in the claim. No new matter is added by way of this amendment. Upon entry of the amendment and response, Claims 73, 78, 81-86, 88-98 and 100 remain pending and are presented for further examination.

B. Objections to the Claims

Claims 92 and 95 are objected to for recitation of non-elected subject matter. Claim 92 recites the method according to Claim 91, wherein the pro-neurotrophin is selected from pro-NGF, pro-BDNF, pro-NT-3 or pro-NT-4/5. Claim 95 recites the method of Claim 93, wherein the Vps10p-domain receptor is selected from SorLA, Sortilin, SorCSI, SorCS2, or SorCS3. In a response to a restriction requirement filed on October 4, 2007, Applicant elected as part of a species election requirement the following species: (i) a neurotrophin: NGF, (ii) a receptor: Sortilin, (iii) a disease: injury and/or dysfunction of the central and/or peripheral nervous system. In the Office communication of September 11, 2007, in requiring the election of these species, the Examiner acknowledged that then-pending Claims 1-4 were generic. The relevant limitations of pending Claim 93 are similarly generic with respect to these species.

> "Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. . . . Upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. 1.141." *See* p. 5, Office communication dated September 11, 2007.

Claims 92 and 95 read on the elected species. In short, the elected subject matter was not subjected to a restriction requirement, and the terms of the election requirement contemplate the possibility of pursuing the additional non-elected species to which the Examiner now objects upon allowance of a generic claim. Applicant therefore respectfully submits that it is premature

at this point to require the removal of the non-elected subject matter from the claims. Withdrawal of the objection is thus requested.

Claim 81 is objected to because line 3 of the claim possesses a period in the middle of the claim. As amended, this inadvertent period is removed from the claim language. As such, this objection is moot.

C. Rejection of Claim 81 Under 35 U.S.C. §112, First Paragraph, Indefiniteness

Claim 81 is rejected under 35 U.S.C. §112, first paragraph as failing to particularly point out and claim the subject matter which the applicants regard as their invention. Specifically, the Examiner states that the claim is "vague and indefinite in that it recites 'nerve damage aberrant sprouting in epilepsy' . . . a condition not know in the art and the metes and bounds are indecipherable." As amended, claim 81 now recites, in part, "necrosis or loss of neurons, nerve damage, aberrant sprouting in epilepsy, and schizophrenia." Nerve damage and aberrant sprouting in epilepsy are art recognized conditions. Thus, the metes and bounds of Claim 81 are decipherable. Applicant respectfully requests the withdrawal of this rejection.

D. Rejection of Claims 73, 78, 81-86, 88-98 and 100 Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 73, 78, 81-86, 88-98 and 100 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicant respectfully disagrees.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' . . . . Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. M.P.E.P. § 2164.08 (citing *In re Buchner*, 929 F.2d 1557 (Fed. Cir. 1993)). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The fact that experimentation may be complex does not necessarily make it undue, if the

art typically engages in such experimentation. M.P.E.P. §2164.01 (citing *In re Certain Limited-Charge Cell culture Microcarriers* 221 USPQ 1165, 1174 (International Trade Commission 1983), *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)).

The Claims

The claims are directed to methods for inhibiting the binding of a pro-neurotrophin to a receptor of the Vps10p-domain receptor family in an animal, wherein the animal suffers from an injury or dysfunction of the central or peripheral nervous system. The methods include exposing said receptor to an amount of antibody that binds the receptor in an amount sufficient to inhibit the receptor, thereby inhibiting a binding interaction between the pro-neurotrophin and the receptor. Accordingly, Claim 93 recites a method for inhibiting the binding of a pro-neurotrophin to a receptor of the Vps10p-domain receptor family in an animal, wherein the animal suffers from an injury or dysfunction of the central or peripheral nervous system, which comprises exposing said receptor to an inhibitorily effective amount of an antibody which binds such a receptor, and thereby inhibits the binding of a pro-neurotrophin to said receptor. Claims 73, 78, 81-86, 88-92 and 94-98 and 100 depend from Claim 93 and thus contain all the features thereof as well as additional features recited in the claims.

The claims satisfy the enablement requirement

In rejecting the claims, the Examiner asserts that:

> In the instant case, one of ordinary skill in the art would have to [1] first correlate Vps10p receptor blockade with the pathology of an injury or dysfunction of the central or peripheral nervous system, [2] develop an antibody that binds said receptor and inhibits the binding of a pro-neurotrophin to said receptor, [3] successfully expose CNS and PNS receptors to said antibody, and [4] demonstrate a useful effect in an animal suffering from an injury or dysfunction . . . .

From this, the Examiner concludes that:

> the instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. . . . Such experimentation is not routine but constitutes undue experimentation.

Applicant disagrees with the basis for the enablement rejections, which appear to address the utility of the invention rather than focus on whether one of skill in the art can make and use the invention as claimed. A 35 U.S.C. §112, first paragraph rejection based on lack of utility should not be imposed or maintained unless an appropriate basis exists for imposing a utility rejection under 35 U.S.C. §101. In other words, Office personnel should not impose a 35 U.S.C. §112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. §101 rejection is proper. M.P.E.P. §2107.01. Nevertheless, solely to address each point raised in the enablement rejection, Applicant respectfully submits the following remarks.

1. Correlation of Vps10p-domain receptor blockade with the pathology of an injury or dysfunction of the central or peripheral nervous system

The Office Action states that "there is no evidence within the art of a nexus between Vsp10p-domain (*sic*) receptor function and disease etiology, pathology or symptomology" and thus, "there is no evidence of record that exposing a receptor of the Vps10p-domain receptor family to an antibody that binds said receptor and subsequently inhibits the binding of a proneurotrophin, would mediate an in vivo effect, as claimed." (*See* Office Action, page 6, lines 8-13.) Furthermore, the Office Action states that "one of ordinary skill in the art would have to first correlate Vps10p receptor blockade with the pathology of an injury or dysfunction of the central or peripheral nervous system." (*See* Office Action, page 6, lines 15-17.) Applicant respectfully disagrees.

As submitted in the Declaration filed March 24, 2008 and submitted again herewith in a second Declaration under Rule 132 ("Declaration") (Appendix A), Applicant carried out *in vivo* experiments in which male rats were subjected to spinal cord injury in the absence or presence of the pro-peptide of pro-NGF. (*See* Declaration, paragraph 7.) In these experiments, the pro-peptide binds sortilin (a Vps10p-domain receptor), thereby acting as a sortilin antagonist and preventing pro-neurotrophins from binding to sortilin. (*See* Declaration, paragraph 8.) In the absence of the pro-peptide sortilin antagonist, 49% of the injured neurons survived. (*See* Declaration, paragraph 9.) In contrast, in the presence of the pro-peptide sortilin antagonist, 67% of the injured neurons survived. (*See* Declaration, paragraph 10.) The results indicate that blockade of this Vps10p-domain receptor has a survival effect on neuronal injury. (*See*

Declaration, paragraph 11.) Accordingly, Applicant respectfully submits that Vps10p-domain receptor blockade clearly has a role in ameliorating the pathology of injury or dysfunction in the central and peripheral nervous system.

Furthermore, the art confirms what Applicant has discovered, namely, that Vps10p-domain receptors, including sortilin, play a role in controlling neuronal survival or cell apoptosis. This has implications for targeting Vps10p blockage in subjects that suffer from symptoms or diseases resulting from injury and dysfunction of the central and peripheral nervous system, including diseases that result from neurodegeneration. For example, pro-NGF-$p75^{NTR}$-sortilin signaling was found to have a role in selective cell death of neurons, which are destroyed in Parkinson's Disease. (*See* Declaration, paragraph 14.) The use of neutralizing antibodies to the prodomain of pro-BDNF or to sortilin was also found to reduce the death of injured sensory neurons *in vitro*; treatment of a neutralizing antibody *in vivo* also increased the number of sensory neurons in the central nervous system. (*See* Declaration, paragraph 15.) Sortilin has been found in basal forebrain neurons, and the presence of antibodies against sortilin was found to be effective in preventing pro-neurotrophin-induced cell death of basal forebrain neurons, which are destroyed in Alzheimer's Disease. (*See* Declaration, paragraph 16.) Accordingly, the art also clearly supports a role for Vps10p-domain receptor signaling in the pathology of injury or dysfunction of the central and peripheral nervous system. (*See* Declaration, paragraph 17.)

In view of the foregoing, Applicant respectfully submits that it is evident from the data submitted herewith and from the art that there is a correlation between Vps10p-domain receptor blockade and the pathology of injury or dysfunction in the central and peripheral nervous systems.

2. Development of an antibody that binds said receptor and inhibits the binding of a pro-neurotrophin to said receptor

The Office Action states that "the instant specification provides no evidence of a single specific antibody that binds to a receptor of the Vps10p-domain receptor family" and that "the specification provides no guidance or working examples of any specific antibody." (*See* Office Action, page 6, lines 4-6 and 13-14.) Applicant respectfully disagrees.

As submitted herewith in the second Declaration under Rule 132 (Appendix B), Applicant developed a sortilin antibody (Nykjaer *et al.* 2004. *Nature* 427:843-848) that is effective in binding the sortilin receptor and inhibiting the binding of a pro-neurotrophin to the receptor. (*See* Declaration, paragraph 18.) Recombinant human sortilin was immobilized in a BIAcore sensorchip, and buffer with or without 10 μg/mL rabbit anti-sortilin antibody (IgG) was applied to separate flow cells on the chip. (*See* Declaration, paragraph 19.) After the buffer was applied, pro-NGF was applied to the separate flow cells and association of pro-NGF binding was measured for 500 seconds. (*See* Declaration, paragraph 20.) The results are illustrated in Appendix B of the Declaration submitted herewith. In the flow cell that was pre-incubated with rabbit anti-sortilin antibody, no binding was observed between proNGF and the immobilized sortilin on the chip. (*See* Declaration, paragraph 21.) In contrast, in the flow cell that was pre-incubated with buffer alone, a strong binding interaction was observed between proNGF and the immobilized sortilin. (*See* Declaration, paragraph 22.) Thus, as illustrated in Appendix B, particularly on Figure B, the results indicate that anti-sortilin antibody was effective in inhibiting binding between pro-NGF and sortilin. (*See* Declaration, paragraph 23.) In view of the results, Applicant respectfully submits that an antibody has been developed in accordance with the disclosure of the instant specification that is effective in inhibiting binding between a pro-neurotrophin and a Vps10p-domain receptor.

Furthermore, one of skill in the art would be able to develop such an antibody in accordance with the disclosure of the instant specification, and such development would not require undue experimentation. As the Examiner acknowledges on page 7 of the Office Action, the skill level in the art is high. Applicant has identified the amino acid sequences of a specific family of receptors containing the Vps10p domain (*e.g.* SEQ ID NOs: 1-5). (*See* Declaration, paragraph 26.) Once provided with a specific sequence (which may encode a specific antigen or

a specific epitope of an antigen), polyclonal and monoclonal antibodies directed against the specific sequence can be produced according to standard procedures. (*See* Declaration, paragraph 27.) Thus, to develop an antibody as described in the instant application would involve routine experimentation that is not beyond the skill of one of ordinary skill and knowledge in the art. (*See* Declaration, paragraph 28.) Accordingly, based on the instant disclosure and knowledge of a person of ordinary skill in the art, the development of the claimed antibody is sufficiently enabled.

In view of the foregoing, Applicant respectfully submits that an antibody that inhibits binding between a pro-neurotrophin and a Vps10p-domain receptor is provided and further, that development of the claimed antibody is sufficiently enabled by the specification.

3. Successful exposure of CNS and PNS receptors to said antibody

The Office Action states that the disclosure does not provide "guidance or direction that the method was successfully achieved in vivo." (*See* Office Action, page 6, lines 14-15.) In addition, while the Examiner acknowledges that "it was known that Vps10p-domain receptors are capable of binding antibodies in vitro" and "does not refute the clinical use of monoclonal antibodies and even specific modifications that may deliver antibodies across the blood brain barrier . . . , in order for an antibody to cross the blood-brain barrier it requires both specificity and modification or engineering. The instant specification fails to identify even one antibody that can be used in the method . . ." (*See* Office Action, page 7, lines 2-13.) Applicant respectfully disagrees.

As an initial matter, the claims do not require peripheral administration or crossing of the blood brain barrier. While peripheral administration of an antibody that is able to cross the blood brain barrier is not excluded, Applicant respectfully submits that the antibody can also be directly administered to the site of injury, thereby bypassing the blood brain barrier. For example, intrathecal administration of antibodies is well-known in the art and is used to treat cancers such as gliomas, melanomas, CNS lymphomas and leptomeningeal tumors as well as experimental autoimmune encephalitis. (*See* Declaration, paragraph 30.) In addition, intracranial administration of antibodies has been investigated for reduction of β-amyloid deposition, of which elevated levels are found in Alzheimer's Disease. (*See* Declaration,

paragraph 31.) The claims do not specify route of administration; rather, they are directed towards methods comprising exposing a Vps10p-domain receptor to an inhibitorily effective amount of an antibody which binds such a receptor. Direct administration of antibody to a site of injury is well-known and used in the art. (*See* Declaration, paragraph 29.) Thus, Applicant respectfully submits that *in vivo* exposure of the receptors to said antibody can be achieved successfully.

Additionally, it is well known in the art that compounds that normally do not cross the blood-brain barrier can be tethered, conjugated or packaged to other components that facilitate the crossing of the barrier. *(See* Declaration, paragraph 32.) Even if one did not employ a direct administration route, targeting of an antibody therapeutic to the brain can be conducted by routine techniques. (*See* Declaration, paragraph 33.) These include fusion protein technology in which an antibody is genetically engineered and expressed as a fusion protein, in which the antibody is fused with a blood brain barrier "molecular Trojan Horse." (*See* Declaration, paragraph 34.) In addition, an antibody can be cationized by covalent modifieation to allow it to penetrate the blood brain barrier. *(See* Declaration, paragraph 35.) As the Examiner acknowledges on page 7 of the Office Action, the skill level in the art is high. Thus, while the amount of experimentation needed to modify the anti-receptor antibody may be high, it is not undue. (*See* Declaration, paragraph 36.)

Furthermore, it is known in the art that the blood brain barrier can become "leaky" during injury or dysfunction of the central or peripheral nervous system, allowing molecules that are too large to cross the intact barrier to gain entry into the nervous system. During pathological conditions, the permeability of the blood brain barrier increases. (*See* Declaration, paragraph 38.) For example, disruption of the blood brain barrier can be a relatively major part of the pathology following cerebral ischemia, and leaking of the blood-brain barrier during such injury or neurodegeneration caused by ischemia can allow passage of compounds that are normally too large to cross the barrier, including antibodies. (*See* Declaration, paragraph 39.) In addition, many brain diseases change the functionality and integrity of the blood brain barrier; this typically results in increased blood brain barrier permeability. (*See* Declaration, paragraph 40.) For example, development of Alzheimer's Disease may be related to impairments of the barrier function of the blood brain barrier, indicating that the blood brain

barrier may have been breached prior to diagnosis of the disease. (*See* Declaration, paragraph 41.) Further, many diseases having an inflammatory component (*e.g.* multiple sclerosis, meningitis, encephalitis, ischemic stroke, head trauma, neurodegenerative diseases, AIDS-related dementia) change the functionality and/or integrity of the blood brain barrier and, accordingly, brain homeostasis. (*See* Declaration, paragraph 42.) In multiple sclerosis, increased blood brain barrier permeability is an early event and further, the barrier is disrupted as a consequence of injury to the nervous system, such as stroke. (*See* Declaration, paragraph 43.) Thus, the art teaches that leaking of the blood brain barrier is a possible consequence of many diseases resulting from injury within the central and peripheral nervous system. Accordingly, an antibody against a Vps10p-domain receptor could cross the blood brain barrier in an animal having an injury or dysfunction in the central or peripheral nervous system even without being engineered to do so. (*See* Declaration, paragraph 44.)

Thus, in view of the foregoing, Applicant respectfully submits that CNS and PNS receptors can be successfully exposed to an administered anti-Vps10p-domain receptor antibody *in vivo*.

4. Demonstration of a useful effect in an animal suffering from an injury or dysfunction

The Office Action states that "the instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution." (*See* Office Action, page 8, lines 13-15.) In the instant case, the Examiner asserts that one of ordinary skill in the art would have to "demonstrate a useful effect in an animal suffering from an injury or dysfunction in order to practice the method as claimed." (*See* Office Action, page 8, lines 20-21.) Applicant has addressed the impropriety of, in effect, rejecting the claims as lacking utility. However, solely to address the Examiner's remarks, Applicant respectfully prevents the remarks below.

Deficiencies under the "useful invention" requirement of 35 U.S.C. §101 will arise in one of two forms. The first is where it is not apparent why the invention is "useful." This can occur when an applicant fails to identify any specific and substantial utility for the invention or fails to disclose enough information about the invention to make its usefulness immediately apparent to

those familiar with the technological field of the invention. *See Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (1966); *In re Fisher*, 421 F.3d 13654, 76 USPQ2d 1225 (Fed. Cir. 2005); *In re Ziegler,* 992 F.2d 1197, 26 USPQ2d 1600 (Fed. Cir. 1993). The second type of deficiency arises in the rare instance where an assertion of specific and substantial utility for the invention made by an applicant is not credible. M.P.E.P. §2107.01.

Applicant has met the requirement of identifying a specific and substantial utility for the invention. The instant disclosure is drawn to compositions which are useful in modulating neurotrophin activity and methods of using the same. Clinically relevant roles of the neurotrophin family are disclosed on pages 2-4 of the instant specification, particularly as they play an important role in neuronal cell survival and differentiation. This has important implications for neuronal cell survival, growth and differentiation in medical conditions where the cells are injured or become apoptotic. For example, propeptides of neurotrophins can differentially activate pro- and anti-apoptotic cellular responses through preferential activation of separate receptors. (*See,* for example, page 3, lines 5-10 of the instant specification.) Neurotrophins are also of clinical interest because they are known to be upregulated under pathological and inflammatory conditions, including those associated with nerve injury and damage to the vascular system. For example, it was demonstrated that proNGF can induce p75 receptor-mediated death of oligodendrocytes following spinal cord injury. (*See,* for example, page 3, lines 15-20 of the instant specification.) Vps10p-domain receptors, including sortilin, are identified as receptors that can bind to the propeptide of neurotrophins with high affinity binding. (*See,* for example, page 4, lines 20-23 of the instant specification.) One of skill in the art would understand from the disclosure that Vps10p-domain receptors, such as sortilin, also have a clinically relevant role in modulating neurotrophin signaling and thus, in influencing neuronal cell survival and differentiation. Accordingly, a specific and substantial utility has been properly identified in the application.

With respect to the credibility of the asserted utility, "[a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of statement of utility or its scope." *In re Langer,* 503 F.2d at 1391,

183 USPQ at 297 (emphasis added). If reasonably correlated to the particular therapeutic or pharmacological utility, **data generated using *in vitro* assays**, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. M.P.E.P. §2107.03, paragraph III (emphasis added). Applicant had described the therapeutic utility of inhibiting binding between a pro-ncurotrophin and a Vps10p-domain receptor in modulating neurotrophin signaling, which has clinical relevance to neuronal cell survival and differentiation. Additionally, Applicant have herewith described and provided *in vitro* data illustrating that anti-sortilin antibody can effectively inhibit binding between pro-NGF and sortilin. Thus, in view of the foregoing, it is not required that Applicant need demonstrate utility in an animal model *in vivo*, and it is respectfully submitted that Applicant's assertion of utility is credible.

In addition to having already met the utility requirements under 35 U.S.C. §101, the data presented in Appendices A and B of the Declaration submitted herewith in totality also illustrate the beneficial effects of using an antibody to inhibit binding between a pro-neurotrophin and a Vps10p-domain receptor. *(See* Declaration, paragraph 24.) The data are presented with respect to the elected species for examination. Briefly, Appendix A illustrates that inhibition of binding between sortilin and pro-NGF leads to increased survival of injured spinal cord neurons in mice. (*See* Declaration, paragraph 11.) Appendix B illustrates that an anti-sortilin antibody can inhibit binding between sortilin and pro-NGF. (*See* Declaration, paragraph 23.) Accordingly, a person of skill in the art would conclude that a useful effect has been demonstrated in the invention and thus sufficiently enabled.

In view of the foregoing remarks, Applicant respectfully submits that the specification teaches one of skill in the art to make and use the claimed subject matter. Thus, it is respectfully submitted that the claims meet the enablement requirement, and withdrawal of the rejection is requested.

Conclusion

Applicant submits that the present Application is in condition for allowance and respectfully request the same. If any issues remain, the Examiner is cordially invited to contact

Applicant's representative at the number provided below in order to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 04-0258.

Respectfully submitted,

Dated: June 15, 2009 By: 

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